MEDICAL UNIVERSITY OF VIENNA

Prenatal alcohol exposure affects specific fetal brain structures – an atlas-based fetal MRI study

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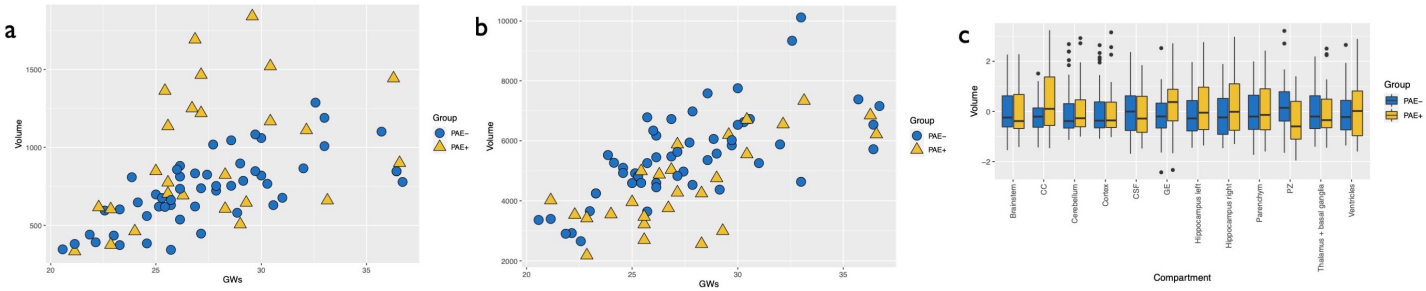

Objective

Numerous postnatal imaging studies have shown structural brain anomalies in patients suffering from Fetal Alcohol Spectrum Disorders, potentially resulting in long-lasting behavioral changes.[1–3] This atlas-based fetal MRI study aimed to identify regional effects of prenatal alcohol exposure (PAE) on human fetal brain development.

Methods and Materials

Women with singleton pregnancy undergoing fetal MRI were prospectively recruited for this IRB approved study from November 2018 until August 2021. All examinations were clinically indicated and referred by local prenatal ultrasound centers. Maternal medical history, gestational ages as determined by ultrasound, and alcohol consumption prior to and during gestation were determined after recruitment utilizing two questionaries (TACE[4] and PRAMS[5]).

Depending on the presence of risk alcohol consumption identified by the questionaries, fetuses were assigned to either the group with (PAE+) or the control group without prenatal alcohol exposure (PAE-). Fetuses exposed to any reported amount of alcohol greater than zero were allocated to the PAE+ group. Only cases with no alcohol exposure throughout the entire pregnancy were allocated to the PAE- group. For statistical analysis, PAE+ fetuses were paired with age-matched PAE- control cases in a 1:2 (PAE+ : PAE-) ratio.

Postprocessing generated super-resolution imaging and semiautomated atlas-based segmentations. After visual inspection, assessment of data quality and manual correction, an atlas-based analysis of twelve fetal brain structures was performed. The investigated brain compartments included the cortex, subcortical parenchyma, periventricular zone (defined as a combination of subventricular and ventricular zone), ganglionic eminence, ventricular system, corpus callosum, deep gray nuclei (basal ganglia and thalamus), brainstem, cerebellum, external cerebrospinal fluid (CSF) spaces, and bilateral hippocampi.

Linear models were applied with an additional factor to account for varying gestational ages and corrected for multiple comparisons using the Benjamini-Hochberg procedure.

Results

A total of 500 women were initially recruited in this study: Overall, 51 fetuses with (PAE+) and 449 without (PAE-) prenatal alcohol exposure were identified. After fetal MRI examination, 27 PAE+ fetuses had to be excluded according to our exclusion criteria for the following reasons: additional complex cerebral anomalies (11), fetal growth restriction (FGR)/placental anomalies (5), confirmed genetic anomalies (confirmed trisomy 13, 1) or poor postprocessing image resolution (10). Thus, 24 PAE+ fetuses (undergoing a total of 26 MRI scans) were finally included in the analyses. In addition, 52 age- and sex-matched PAE- fetuses (undergoing a total of 52 MRI scans) without structural brain anomalies were selected for the PAE- control group to achieve a 1:2 matching ratio. Gestational ages ranged from 21-37 weeks (mean 27.4 GW) and matching was performed with a maximum age difference of four gestational days.

Linear mixed effect models of the volume of each segmented structure revealed a significant effect for PAE status on the corpus callosum volume ($p < 0.001$, 0.95 CI [99.29 – 346.45]) and on the volume of the periventricular zone ($p = 0.001$, 0.95 CI [-1408.05 – -381.57]) that survived multiple comparison correction at $q = 0.006$ each. Thus, a statistically significant volume increased volume of the corpus callosum and a decreased volume of the periventricular zone was identified. Models for the remaining structures did not show a significant effect of the PAE status on the volumes.

Conclusion

This study systematically documented the selective effects of PAE on regional brain volumes at prenatal stages: Besides the volumetric reduction of the periventricular zone, an increased regional growth of the corpus callosum was found indicating a change in the developmental dynamics of the normal trajectory of interhemispheric connectivity - even with minor prenatal alcohol exposure (1-3 standardized drinks/week).

Funding

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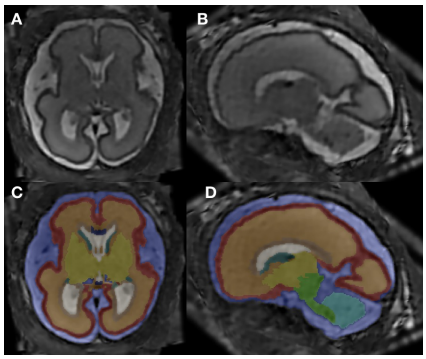

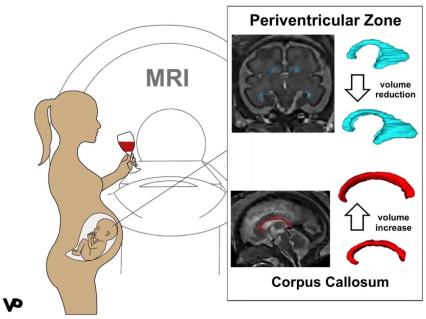

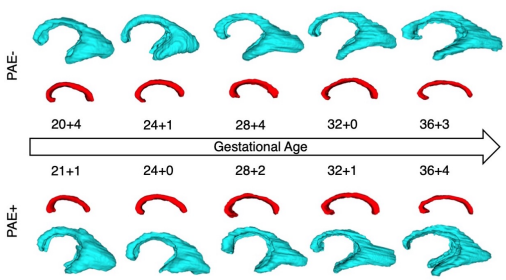

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Figures

Top row: Volumes of the corpus callosum **(left - a)** and the periventricular zone **(middle - b)** given in mm^3 and gestational weeks (GW). Comparison of all investigated compartments **(right - c)**: Volumes of brainstem, corpus callosum (CC), cerebellum, cortex, external cerebrospinal fluid (CSF) spaces, ganglionic eminence (GE), left and right hippocampus, subcortical parenchyma, periventricular zone (PZ), deep grey nuclei (thalamus and basal ganglia), and ventricular system throughout gestation. Color coding: yellow – PAE+ group, blue – PAE- group

Bottom row: Postprocessed MRI super-resolution reconstructions in axial and sagittal planes of a fetus at 26+6 GW **(left - a, b)**. Respective manually corrected atlas-based tissue segmentation. **(left – c, d)**. Effects of prenatal alcohol exposure: 3D-modelling of the periventricular zone and the corpus callosum **(middle)**. Longitudinal growth trajectories of the periventricular zone and the corpus callosum in fetuses with (PAE+) and without (PAE-) prenatal alcohol exposure. Color coding: blue – periventricular zone, red – corpus callosum